

## PCT JT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
 US Department of Commerce  
 United States Patent and Trademark  
 Office, PCT  
 2011 South Clark Place Room  
 CP2/5C24  
 Arlington, VA 22202  
 ETATS-UNIS D'AMERIQUE  
 in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 13 February 2001 (13.02.01)	
<b>International application No.</b> PCT/EP00/05181	<b>Applicant's or agent's file reference</b> 0099216-Bzmi
<b>International filing date</b> (day/month/year) 06 June 2000 (06.06.00)	<b>Priority date</b> (day/month/year) 12 June 1999 (12.06.99)
<b>Applicant</b> KORDOWICZ, Maria et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
 13 December 2000 (13.12.00)

☐ in a notice effecting later election filed with the International Bureau on:  
 \_\_\_\_\_

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  Zakaria EL KHODARY  Telephone No.: (41-22) 338.83.38
---	--

## PATENT COOPERATION TREATY

## PCT

## NOTIFICATION RELATING TO PRIORITY CLAIM

(PCT Rules 26bis.1 and 26bis.2 and  
Administrative Instructions, Sections 402 and 409)

From the INTERNATIONAL BUREAU

To:

MERCK PATENT GMBH  
D-64271 Darmstadt  
ALLEMAGNE

Date of mailing (day/month/year) 30 October 2000 (30.10.00)	
Applicant's or agent's file reference 0099216-Bzmi	<b>IMPORTANT NOTIFICATION</b>
International application No. PCT/EP00/05181	International filing date (day/month/year) 06 June 2000 (06.06.00)
Applicant MERCK PATENT GMBH et al	

The applicant is hereby **notified** of the following in respect of the priority claim(s) made in the international application.

1. ☒ **Correction of priority claim.** In accordance with the applicant's notice received on: **02 October 2000 (02.10.00)**, the following priority claim has been corrected to read as follows:  

**EP 12 June 1999 (12.06.99) 99111468.7**

☐ even though the indication of the number of the earlier application is missing.

☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:
2. ☐ **Addition of priority claim.** In accordance with the applicant's notice received on: , the following priority claim has been added:  

☐ even though the indication of the number of the earlier application is missing.

☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:
3. ☐ As a **result of the correction and/or addition** of (a) priority claim(s) under items 1 and/or 2, the (earliest) priority date is:
4. ☐ **Priority claim considered not to have been made.**

☐ The applicant failed to respond to the Invitation under Rule 26bis.2(a) (Form PCT/IB/316) within the prescribed time limit.

☐ The applicant's notice was received after the expiration of the prescribed time limit under Rule 26bis.1(a).

☐ The applicant's notice failed to correct the priority claim so as to comply with the requirements of Rule 4.10.

The applicant may, before the technical preparations for international publication have been completed and subject to the payment of a fee, request the International Bureau to publish, together with the international application, information concerning the priority claim. See Rule 26bis.2(c) and the PCT Applicant's Guide, Volume I, Annex B2(IB).
5. ☐ In case where **multiple priorities** have been claimed, the above item(s) relate to the following priority claim(s):
6. A copy of this notification has been sent to the receiving Office and
 

☒ to the International Searching Authority (where the international search report has not yet been issued).

☒ the designated Offices (which have already been notified of the receipt of the record copy).

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No. (41-22) 740.14.35</p>	<p>Authorized officer</p> <p style="text-align: right;">Kari Huynh-Khuong</p> <p>Telephone No. (41-22) 338.83.38</p>
---	--

PCT

REC'D 14 SEP 2001



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 0099216-Bzmi	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP00/05181	International filing date (day/month/year) 06/06/2000	Priority date (day/month/year) 12/06/1999
International Patent Classification (IPC) or national classification and IPC C12N15/52		
Applicant MERCK PATENT GMBH		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 6 sheets, including this cover sheet.  
  
☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  
  
 These annexes consist of a total of sheets.

- This report contains indications relating to the following items:
  - I ☒ Basis of the report
  - II ☐ Priority
  - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☐ Lack of unity of invention
  - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI ☐ Certain documents cited
  - VII ☐ Certain defects in the international application
  - VIII ☒ Certain observations on the international application

Date of submission of the demand  13/12/2000	Date of completion of this report  11.09.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Sommer, B  Telephone No. +49 89 2399 7099  

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05181

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*)  
**Description, pages:**

1-30 as originally filed

### Claims, No.:

1-20 as originally filed

### Drawings, sheets:

1/13-13/13 as originally filed

### Sequence listing part of the description, pages:

1-15, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP00/05181

- ☐ the description,      pages:  
☐ the claims,      Nos.:  
☐ the drawings,      sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	1-17, 20
	No:	Claims	18, 19
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1- 20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations  
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/05181

**Re Item V**

1. Reference is made to the following documents:

D1: EP-A-0 193 330, cited in the application

D2: US-A-5 827 721

D3: JONES C. P. AND SAWYER R. T.: 'Heparin inhibits mammalian, but not leech hyaluronidase.' THROMBIN RESEARCH, vol. 55, no. 6, 1989, pages 791-796

2. The present application concerns a hyaluronidase from the leech species Hirudinaria manillensis having a molecular weight of 53-60 dependent on glycosylation, an isolation and purification process for said enzyme, a DNA coding for it, a recombinant protein with hyaluronidase activity, an expression vector, a host cell as well as a pharmaceutical composition comprising said protein and its use in the manufacture of a medicament for treating myocardial, cardiovascular and thrombotic disorders and tumors.

3. In view of the documents cited in the ISR, only the subject-matter of claims 1-17 and 20 has to be regarded as being novel in the sense of **Article 33(2) PCT**.

Claims 18 and 19 referring to pharmaceutical compositions comprising additionally a pharmaceutically active compound or heparin, respectively, are objected to as lacking novelty as pharmaceutical compositions in general as well as pharmaceutical compositions comprising heparin are well known formulations in the art and widely used in medical treatment.

4. Claims 1-17 and 20 are objected to for the following reasons as they do not appear to involve an inventive step (**Article 33(3) PCT**):

Document D1, which is considered as closest prior art, discloses hyaluronidases having a molecular weight of 28.5 kDa, which were isolated from Hirudinaria manillensis and Poecilobdella granulosa, leech species of the same subfamily of Hirudinariinae. The subject-matter of claims 1-4 and 6 differ from D1 by a molecular weight of 53-60 kDa dependent on glycosylation, an isoelectric point of 7.2-8.0 or a specific activity of >100 kU/mg protein, respectively.

The problem to be solved by the present invention may be regarded as providing an alternative hyaluronidase from Hirudinaria manillensis. However, a SDS-PAGE of a purified hyaluronidase preparation in D1 reveals in addition to the protein of 28.5 kDa

disclosed in the document a band of approx. 60 kDa (D1, Fig. 4, lane 4). As the molecular weight is only a non-limiting parameter and not sufficient to distinguish a protein unambiguously from the prior art, the 60 kDa band in D1 might correspond to the enzyme of the present application. Even if it is not the case, D1 indicates at least the presence of further hyaluronidases with higher molecular weight in Hirudinariinae.

In order to solve the technical problem, a skilled person would try to isolate such proteins using common techniques and arrive at the subject-matter of claims 1-4 and 6 in an obvious way. The same applies to claim 5, because its subject-matter can be obtained by simply sequencing the isolated protein.

Furthermore, D1 discloses the preparation of a crude extract by homogenising the leech heads and ammonium sulphate precipitation followed by gel chromatography.

The subject-matter of claim 7 concerning the process of hyaluronidase purification differs from this disclosure in purifying the crude extract via various additional chromatography steps. However, a skilled person trying to solve the technical problem, i.e. looking for a purification method for crude hyaluronidase extracts, would have knowledge of D2, where the same order of chromatographic columns is used to isolate a hyaluronidase from bovine testicular extracts (D2, example 1). He/she would immediately combine the teaching of both documents and arrive at the subject-matter of claims 7-9 in an obvious way.

Claims 10-15 are also lacking an inventive step, because said claims add only subject-matter which is obtainable by workshop modifications.

Claims 16, 17 and 20 referring to a pharmaceutical composition comprising the enzyme and its use for the manufacture of a medicament are objected to as lacking inventivity. Besides the fact, that D1 describes the use of leech hyaluronidase in pharmaceutical therapy for myocardial ischemia, thrombosis or tumors (D1, page 6, line 33 - page 8, line 12), Document D3 explicitly discloses that leech hyaluronidase is superior for the treatment of myocardial disorders and thrombi than mammalian enzymes, because it can be used in combination with heparin (D3, page 791, last paragraph).

Therefore, none of claims 1-17 or 20 meets the requirements of **Article 33(3) PCT**.

Re Item VIII

5. Claims 1-4, 6, 16, 18 and 19 are objected to as lacking clarity according to **Article 6 PCT** for the following reasons:

Claims 1-4 and 6 are drawn to a leech hyaluronidase having a molecular weight of 53-60 dependent on glycosylation, an isoelectric point of 7.2-8.0 or a specific enzymatic activity of >100 kU/mg protein, respectively. However, these parameters alone are not sufficient to characterise the subject-matter of said claims unambiguously and to distinguish it from the prior art.

Claim 16 referring to a protein as a medicament dose not meet the requirements of **Article 6 PCT** in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added.

Claims 18 and 19 referring to pharmaceutical compositions in general are not supported by the description as their scope is broader than justified by the description and drawings. Moreover, the matter for which protection is sought is completely unclear. A skilled person is not enabled to determine which technical features are necessary to perform the invention.



# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>0099216-Bzmi</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/EP 00/ 05181</b>	International filing date (day, month, year) <b>06/06/2000</b>	(Earliest) Priority Date (day, month, year) <b>12/06/1999</b>
Applicant <b>MERCK PATENT GMBH</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

### 1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

# INTERNATIONAL SEARCH REPORT

ational application No.  
PCT/EP 00/05181

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

Line 02 in the text, please remove the word "novel".

Line 03 in the text, please remove the word "new".

## INTERNATIONAL SEARCH REPORT

International Application No.

PC 00/05181

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/52 C12N9/26 A61K38/43

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EMBASE, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 193 330 A (BIOPHARM LTD) 3 September 1986 (1986-09-03) cited in the application the whole document ---	1-4, 6, 8, 9, 16, 17, 20
A	JONES C. P. AND SAWYER R. T.: "Heparin inhibits mammalian, but not leech hyaluronidase." THROMBIN RESEARCH, vol. 55, no. 6, 1989, pages 791-796, XP000953413 the whole document ---	1-20
A	US 5 827 721 A (FORMBY BENT ET AL) 27 October 1998 (1998-10-27) column 6, line 24 - line 61; example 1 -----	7

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

1 November 2000

Date of mailing of the international search report

15/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel: (+31-70) 340-2040, Tx: 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Mandl, B

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC 00/05181

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0193330 A	03-09-1986	DE 3688710 A	26-08-1993
		DE 3688710 T	18-11-1993
		US 4820516 A	11-04-1989
-----			
US 5827721 A	27-10-1998	US 5747027 A	05-05-1998
		WO 9631596 A	10-10-1996
-----			